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The vaccination program against avian influenza: A mathematical approach

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Abstract

It was reported that a vaccination program against avian influenza executed in China eradicated a dominant avian flu virus but led to a prevalence of predominant avian flu virus. Interestingly, the change of the prevalence could occur in other countries where the vaccination program was not executed. The mechanism for the emergence and prevalence of predominant virus is still unknown. In this study, we construct and analyze a mathematical model to investigate the mechanism.

1 Introduction

In China, despite a compulsory program for the vaccination of all poultry commencing, H5N1 influenza virus has caused outbreaks in poultry in 12 provinces. Epidemiological analysis showed that H5N1 influenza viruses were continued to be perpetuated in poultry in each of the provinces tested, mainly in domestic duck and geese. Interestingly, genetic analysis revealed that an H5N1 influenza variant (Fujian-like) had emerged and become prevalent variant in each of the provinces, replacing those previously established multiple sublineages in different regions of southern China. Some data indicate that seroconversion rates are still low and that poultry are poorly immunized against FJ-like viruses, which suggests that the poultry vaccine currently used in China may only generate very low neutralizing antibodies to FJ-like viruses in comparison to other previously cocirculating H5N1 sublineages ([9]). This situation can help to select for the FJ-like sublineage in poultry. To investigate the change of prevalent strain we propose the following simple mathematical model:

$$\begin{aligned}X_1' &= (1-p)c - (b+e)X_1 - (\omega_1 Y_1 + \phi_1 Z_1)X_1, \\V_1' &= pc - (b+e)V_1 - \sigma \phi_1 Z_1 V_1, \\Y_1' &= \omega_1 Y_1 X_1 - (b+m_y)Y_1, \\Z_1' &= \phi_1 Z_1 (X_1 + \sigma V_1) - (b+m_z)Z_1.\end{aligned}\tag{1}$$

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In the model, X_1 , V_1 , Y_1 and Z_1 denote susceptible birds, vaccinated birds against dominant strain, infected birds with dominant avian flu strain and infected bird with predominant avian flu strain, respectively. The parameter c is the rates at which new birds are born. At the beginning of vaccination program, X_1 directly moves to V_1 by the vaccination to susceptible birds. However, after some vaccinated period, the direct movement may vanish because almost all birds are vaccinated. Thereafter, the vaccination is only administered to the new born birds. In order to simplify the vaccination program we consider only the vaccination to the new born birds because the direct movement by the vaccination program can be expressed by some choice of initial value. The new born birds are vaccinated at the rate $0 \leq p \leq 1$ and the vaccinated individuals can completely protect from the dominant strain and partial protect from the predominant strain at the rate $0 \leq 1 - \sigma \leq 1$ (for example, $\sigma = 0$ represents complete cross immunity against dominant and predominant strains). The parameter b is the natural death rate and e is the dispersal or export rate. We consider that only susceptible and vaccinated birds can be dispersed or exported because the avian flu viruses can cause severe illness and high mortality in poultry. Further m_y and m_z are the additional death rate mediated by avian flu. The parameters ω_1 and ϕ_1 are the transmission rate of dominant and predominant avian flu strains, respectively. For instance, we can consider that the dominant avian flu strain represents current vaccine strain in poultry and the predominant avian flu strain represents FJ-like viruses which has emerged and are selected when the vaccination program is executed ([9]).

Further the FJ-like viruses have already transmitted to Hong Kong, Laos, Malaysia and Thailand, resulting in a new transmission and outbreak wave in Southeast Asia. It is strange that the FJ-like viruses become prevalent strain in no-vaccinated area because the dominant strain prevailed before the initiation of the vaccination program executed in other areas. The mechanism for the emergence and prevalence of the FJ-like virus over a large geographical region within a short period is still unknown. It is said that one possibility is an effect of carrier wild birds: Origins could be traced by using probes of various regions of the new isolates and this analysis indicated many contained regions that traced back to wild bird isolates in Hong Kong in 2003, or isolates from northern China in 2003. These data indicate wild birds are responsible for the transport and transmission of the evolving H5N1. However, in this paper, we investigate the another possibility of the emergence and prevalence by a mathematical model. Based on concerns about highly pathogenic avian influenza H5N1 virus and its potential to cause illness in humans, CDC and the U.S. Department of Agriculture have taken steps to prevent importation of birds and unprocessed bird products from countries with the virus in domestic poultry ([4]). However it is impossible for government to control the importation completely because

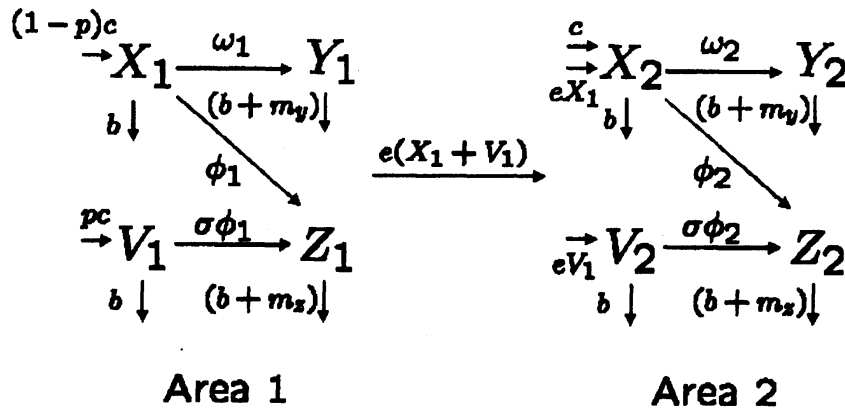


Figure 1: Model schematic showing the vaccination program and the illegal trade or dispersal in poultry from Area 1 to Area 2

of some smuggler. For example, in some outbreaks, the tendency to hide or smuggle especially valuable birds, such as fighting cocks, can also help maintain the virus in the environment or contribute to its further geographical spread ([10]). Therefore, we have to consider the effect of the export or dispersal of domestic poultry. Remember that only susceptible and vaccinated birds can be dispersed or exported because the avian flu viruses can cause severe illness and high mortality in poultry. We assume that the vaccination program is executed in Area 1 (such as China) but the program is not executed in Area 2 (such as Malaysia, Vietnam and Thailand) and both susceptible and vaccinated birds export or disperse from Area 1 to Area 2 (see Fig. 1). These assumptions lead to the following mathematical model:

$$\begin{aligned}
 X_1' &= (1-p)c - (b+e)X_1 - (\omega_1 Y_1 + \phi_1 Z_1)X_1, \\
 V_1' &= pc - (b+e)V_1 - \sigma \phi_1 Z_1 V_1, \\
 Y_1' &= \omega_1 Y_1 X_1 - (b+m_y)Y_1, \\
 Z_1' &= \phi_1 Z_1 (X_1 + \sigma V_1) - (b+m_z)Z_1, \\
 X_2' &= c + eX_1 - bX_2 - (\omega_2 Y_2 + \phi_2 Z_2)X_2, \\
 V_2' &= eV_1 - bV_2 - \sigma \phi_2 Z_2 V_2, \\
 Y_2' &= \omega_2 Y_2 X_2 - (b+m_y)Y_2, \\
 Z_2' &= \phi_2 Z_2 (X_2 + \sigma V_2) - (b+m_z)Z_2.
 \end{aligned} \tag{2}$$

In the model, X_i , V_i , Y_i and Z_i denote susceptible birds, vaccinated birds against dominant strain, infected birds with dominant avian flu strain and infected bird with predominant avian flu strain in Area i ($i = 1, 2$), respectively. The parameters ω_i and ϕ_i are the transmission rate of dominant and predominant avian flu strains in Area i , respectively. Further the meaning of the other parameters is the same as (1). For more detailed

discussion of this model, see [8].

2 Mathematical properties

In order to investigate the change of prevalence strain in Area 1 and 2 by the vaccination program we have to demonstrate the mathematical properties of model (2). We remark that the dynamics in Area 1 are independent of those in Area 2. Therefore we can obtain the dynamical properties in Area 1 from only model (1). Once we obtain the properties in Area 1, we can easily understand those in Area 2 by a similar method in *Theorem A.1* of [5].

2.1 The disease transmission in Area 1

To understand the dynamics of the disease transmission in Area 1 we firstly analyze model (1) and divide the analysis into three situations concerned with the vaccination rate as follows;

(a) *No vaccination program: $p = 0$ in Area 1*

If the vaccination rate $p = 0$ (No vaccination program), then model (1) is

$$\begin{aligned} X_1' &= c - (b + e)X_1 - (\omega_1 Y_1 + \phi_1 Z_1)X_1, \\ V_1' &= -(b + e)V_1 - \sigma\phi_1 Z_1 V_1, \\ Y_1' &= \omega_1 Y_1 X_1 - (b + m_y)Y_1, \\ Z_1' &= \phi_1 Z_1 (X_1 + \sigma V_1) - (b + m_z)Z_1. \end{aligned} \tag{3}$$

It is clear that $\lim_{t \rightarrow \infty} V_1(t) = 0$ and this system has the following three possible equilibria:

$$\begin{aligned} E_1^{n0} &= (X_1^{n0}, 0, 0, 0), \text{ where } X_1^{n0} = \frac{c}{b + e}; \\ E_1^{nd} &= (X_1^{nd}, 0, Y_1^{nd}, 0), \text{ where } X_1^{nd} = \frac{b + m_y}{\omega_1}, Y_1^{nd} = \frac{c - (b + e)X_1^{nd}}{\omega_1 X_1^{nd}}; \\ E_1^{np} &= (X_1^{np}, 0, 0, Z_1^{np}), \text{ where } X_1^{np} = \frac{b + m_z}{\phi_1}, Z_1^{np} = \frac{c - (b + e)X_1^{np}}{\phi_1 X_1^{np}}. \end{aligned}$$

Note that model (3) is typical competitive system for multiple infectious strains which leads to competitive exclusion ([1]-[3], [7]). The dynamics of (3) are completely determined by the so-called basic reproductive number of the dominant and predominant strains, respectively ([7]):

$$R_1^{nd} = \frac{\omega_1}{b + m_y} X_1^{n0}, \quad R_1^{np} = \frac{\phi_1}{b + m_z} X_1^{n0}.$$

Clearly E_1^{n0} always exists, E_1^{nd} exists iff $R_1^{nd} > 1$ and E_1^{np} exists iff $R_1^{np} > 1$. Further, to simply understand a concept of competition between the strains we introduce the another basic reproductive numbers ([6]):

$$\bar{R}_1^{nd} = \frac{\omega_1}{b + m_y} X_1^{np}, \quad \bar{R}_1^{np} = \frac{\phi_1}{b + m_z} X_1^{nd}.$$

We remark that R_1^{nd} (R_1^{np}) represents an average number of the infected birds with the dominant (predominant) avian flu by a single infected bird with the dominant (predominant) strain under the condition that all birds are susceptible, but \bar{R}_1^{nd} (\bar{R}_1^{np}) is the basic reproduction number after a spread of predominant (dominant) strain in the bird world. Note that $\bar{R}_1^{nd} \bar{R}_1^{np} = 1$. Further these basic reproductive numbers have the following relations:

Remark 2.1. $R_1^{nd} > R_1^{np}$ ($R_1^{np} > R_1^{nd}$) is equivalent to $\bar{R}_1^{np} < 1$ ($\bar{R}_1^{nd} < 1$) and $\bar{R}_1^{nd} < 1$ ($\bar{R}_1^{np} < 1$) is equivalent to $\bar{R}_1^{np} > 1$ ($\bar{R}_1^{nd} > 1$).

The dynamical properties of model (3) are given by the following theorem:

Theorem 2.1. (i) If $R_1^{nd} \leq 1$ and $R_1^{np} \leq 1$, then E_1^{n0} is globally asymptotically stable (GAS) which means that the orbit converges to the equilibrium as $t \rightarrow \infty$ for arbitrary initial point.

(ii) If $R_1^{nd} > 1$ and $\bar{R}_1^{np} < 1$, then E_1^{nd} is GAS.

(iii) If $R_1^{np} > 1$ and $\bar{R}_1^{nd} < 1$, then E_1^{np} is GAS.

The proofs of this Theorem are given in [7] (see its Theorem 3.1.).

(b) Complete vaccination program: $p = 1$ in Area 1

If the vaccination rate $p = 1$ (Complete vaccination program), then model (1) is

$$\begin{aligned} X_1' &= -(b + e)X_1 - (\omega_1 Y_1 + \phi_1 Z_1)X_1, \\ V_1' &= c - (b + e)V_1 - \sigma \phi_1 Z_1 V_1, \\ Y_1' &= \omega_1 Y_1 X_1 - (b + m_y)Y_1, \\ Z_1' &= \phi_1 Z_1 (X_1 + \sigma V_1) - (b + m_z)Z_1. \end{aligned} \tag{4}$$

It is clear that $\lim_{t \rightarrow \infty} X_1(t) = 0$ and $\lim_{t \rightarrow \infty} Y_1(t) = 0$ and this system has the following two equilibria:

$$\begin{aligned} E_1^{c0} &= (0, V_1^{c0}, 0, 0), \quad \text{where } V_1^{c0} = \frac{c}{b + e}; \\ E_1^{cp} &= (0, V_1^{cp}, 0, Z_1^{cp}), \quad \text{where } V_1^{cp} = \frac{b + m_z}{\sigma \phi_1}, \quad Z_1^{cp} = \frac{c - (b + e)V_1^{cp}}{\sigma \phi_1 V_1^{cp}}. \end{aligned}$$

This system (4) is essentially 2-dimensional and the dynamics is clear ([5]). The basic reproductive number of predominant strain is given by

$$R_1^{cp} = \frac{\sigma\phi_1}{b+m_z} V_1^{c0}.$$

Clearly E_1^{c0} always exists and E_1^{cp} exists iff $R_1^{cp} > 1$. The dynamical properties of model (4) are given by the following theorem:

Theorem 2.2. (i) If $R_1^{cp} \leq 1$, then E_1^{c0} is GAS.

(ii) If $R_1^{cp} > 1$, then E_1^{cp} is GAS.

The proofs of this Theorem are given in [5] (see its *Theorems 3.1*).

(c) *Incomplete vaccination program: $0 < p < 1$ in Area 1*

If the vaccination rate $0 < p < 1$ (Incomplete vaccination program), then we have to consider system (1) directly. This system has the following four possible equilibria:

$$\begin{aligned} E_1^{i0} &= (X_1^{i0}, V_1^{i0}, 0, 0), \text{ where } X_1^{i0} = \frac{(1-p)c}{b+e}, V_1^{i0} = \frac{pc}{b+e}; \\ E_1^{id} &= (X_1^{id}, V_1^{id}, Y_1^{id}, 0), \text{ where } X_1^{id} = \frac{b+m_y}{\omega_1}, V_1^{id} = \frac{pc}{b+e}, Y_1^{id} = \frac{(1-p)c - (b+e)X_1^{id}}{\omega_1 X_1^{id}}; \\ E_1^{ip} &= (X_1^{ip}, V_1^{ip}, 0, Z_1^{ip}), \text{ where } X_1^{ip} = \frac{(1-p)c}{b+e+\phi_1 Z_1^{ip}}, V_1^{ip} = \frac{pc}{b+e+\sigma\phi_1 Z_1^{ip}} \end{aligned}$$

and Z_1^{ip} is the unique root of the following equation:

$$\frac{\phi_1(1-p)c}{b+e+\phi_1 Z_1} + \frac{\sigma\phi_1 pc}{b+e+\sigma\phi_1 Z_1} = b+m_z; \quad (5)$$

$$\begin{aligned} E_1^{i+} &= (X_1^{i+}, V_1^{i+}, Y_1^{i+}, Z_1^{i+}), \text{ where } X_1^{i+} = \frac{b+m_y}{\omega_1}, V_1^{i+} = \frac{1}{\sigma} \left(\frac{b+m_z}{\phi_1} - \frac{b+m_y}{\omega_1} \right), \\ Y_1^{i+} &= \frac{1}{\omega_1} \left\{ \frac{(1-p)c - (b+e)X_1^{i+}}{X_1^{i+}} - \phi_1 Z_1^{i+} \right\}, Z_1^{i+} = \frac{pc - (b+e)V_1^{i+}}{\sigma\phi_1 V_1^{i+}}. \end{aligned}$$

We also introduce the two basic reproductive numbers of dominant and predominant strains;

$$\begin{aligned} R_1^{id} &= \frac{\omega_1}{b+m_y} X_1^{i0}, \quad R_1^{ip} = \frac{\phi_1}{b+m_z} X_1^{i0} + \frac{\sigma\phi_1}{b+m_z} V_1^{i0}, \\ \bar{R}_1^{id} &= \frac{\omega_1}{b+m_y} X_1^{ip}, \quad \bar{R}_1^{ip} = \frac{\phi_1}{b+m_z} X_1^{id} + \frac{\sigma\phi_1}{b+m_z} V_1^{id}. \end{aligned}$$

The meaning of these numbers is the same as R_1^{nd} , R_1^{np} , \bar{R}_1^{nd} and \bar{R}_1^{np} in (a). It is clear that E_1^{i0} always exists and E_1^{id} exists iff $R_1^{id} > 1$. From equation (5), the existence condition of E_1^{ip} is given by

$$b + m_z < \frac{\phi_1(1-p)c + \sigma\phi_1pc}{b+e} \iff 1 < R_1^{ip}.$$

Further, let F be the following function of X_1 :

$$F(X_1) = (b+e)\phi_1 \left(1 - \frac{1}{\sigma}\right) X_1^2 - \left\{ (b+e)(b+m_z) \left(1 - \frac{1}{\sigma}\right) + \phi_1c \right\} X_1 + (1-p)c(b+m_z).$$

Then we obtain the following existence condition of E_1^{i+} ;

$$\frac{b+m_z}{\phi_1} - \frac{pc\sigma}{b+e} < X_1^{i+} < \frac{b+m_z}{\phi_1}, \quad 0 < F(X_1^{i+}).$$

Since $0 < F(0)$, $0 > F(\frac{b+m_z}{\phi_1})$ and $F''(X_1) < 0$, we can obtain the following relation;

$$\frac{b+m_z}{\phi_1} - \frac{pc\sigma}{b+e} < X_1^{i+} < \frac{b+m_z}{\phi_1}, \quad 0 < F(X_1^{i+}) \iff \max \left\{ 0, \frac{b+m_z}{\phi_1} - \frac{pc\sigma}{b+e} \right\} < X_1^{i+} < X_1^*$$

where X_1^* is the larger root of $F(X_1) = 0$. From straightforward but tedious calculations, we can evaluate $X_1^* = X_1^{ip}$. This implies that

$$\max \left\{ 0, \frac{b+m_z}{\phi_1} - \frac{pc\sigma}{b+e} \right\} < X_1^{i+} < X_1^* \iff 1 < \bar{R}_1^{id}, \quad 1 < \bar{R}_1^{ip}.$$

In this way, we can conclude the existence conditions of these equilibria in the following lemma.

Lemma 2.1. (i) E_1^{i0} always exists in \mathbb{R}_+^4 .

(ii) E_1^{id} exists in \mathbb{R}_+^4 iff $1 < R_1^{id}$.

(iii) E_1^{ip} exists in \mathbb{R}_+^4 iff $1 < R_1^{ip}$.

(iv) E_1^{i+} exists in \mathbb{R}_+^4 iff $1 < \bar{R}_1^{id}$ and $1 < \bar{R}_1^{ip}$.

Here we have to note the relation between the basic reproductive numbers in the following Lemma 2.2.

Lemma 2.2. $\bar{R}_1^{id} < 1 < R_1^{id}$ and $\bar{R}_1^{ip} < 1 < R_1^{ip}$ can not hold simultaneously.

Remark 2.2. Lemma 2.2 can be proved directly by tedious and complex analysis but it will be clear in Theorem 2.3.

The dynamical properties of model (1) are given by the following theorem:

Theorem 2.3. (i) If $R_1^{id} \leq 1$ and $R_1^{ip} \leq 1$, then E_1^{i0} is GAS.

(ii) If $R_1^{id} > 1$ and $\bar{R}_1^{ip} \leq 1$, then E_1^{id} is GAS.

(iii) If $R_1^{ip} > 1$ and $\bar{R}_1^{id} \leq 1$, then E_1^{ip} is GAS.

(iv) If $\bar{R}_1^{id} > 1$ and $\bar{R}_1^{ip} > 1$, then E_1^{i+} is GAS.

Proof. (i) Let us consider the Lyapunov function

$$V_0 = X_1 - X_1^{i0} \log X_1 + V_1 - V_1^{i0} \log V_1 + Y_1 + Z_1.$$

We have

$$\begin{aligned} \dot{V}_0 &= (X_1 - X_1^{i0}) \left\{ \frac{(1-p)c}{X_1} - (b+e) - \omega_1 Y_1 - \phi_1 Z_1 \right\} + (V_1 - V_1^{i0}) \left\{ \frac{pc}{V_1} - (b+e) - \sigma \phi_1 Z_1 \right\} \\ &\quad + Y_1 \{ \omega_1 X_1 - (b+m_y) \} + Z_1 \{ \phi_1 (X_1 + \sigma V_1) - (b+m_z) \} \\ &= (1-p)c \left(2 - \frac{X_1^{i0}}{X_1} - \frac{X_1}{X_1^{i0}} \right) + pc \left(2 - \frac{V_1^{i0}}{V_1} - \frac{V_1}{V_1^{i0}} \right) + \omega_1 Y_1 \left(X_1^{i0} - \frac{b+m_y}{\omega_1} \right) \\ &\quad + \phi_1 Z_1 \left(X_1^{i0} + \sigma V_1^{i0} - \frac{b+m_z}{\phi_1} \right). \end{aligned}$$

We remark that $X_1^{i0} - (b+m_y)/\omega_1 \leq 0$ iff $R_1^{id} \leq 1$ and $X_1^{i0} + \sigma V_1^{i0} - (b+m_z)/\phi_1 \leq 0$ iff $R_1^{ip} \leq 1$. Further it is clear that

$$2 - \frac{X_1^{i0}}{X_1} - \frac{X_1}{X_1^{i0}} \leq 0, \quad 2 - \frac{V_1^{i0}}{V_1} - \frac{V_1}{V_1^{i0}} \leq 0$$

because the arithmetic mean is larger than, or equals to the geometric mean. Therefore $\dot{V}_0 \leq 0$ because $R_1^{id} \leq 1$ and $R_1^{ip} \leq 1$, and we can conclude that by the Lyapunov-LaSalle's invariance principle, all the trajectories of (1) converges to E_1^{i0} .

(ii) Let us consider the Lyapunov function

$$V_d = X_1 - X_1^{id} \log X_1 + V_1 - V_1^{id} \log V_1 + Y_1 - Y_1^{id} \log Y_1 + Z_1.$$

Then

$$\begin{aligned} \dot{V}_d &= (X_1 - X_1^{id}) \left\{ \frac{(1-p)c}{X_1} - (b+e) - \omega_1 Y_1 - \phi_1 Z_1 \right\} + (V_1 - V_1^{id}) \left\{ \frac{pc}{V_1} - (b+e) - \sigma \phi_1 Z_1 \right\} \\ &\quad + (Y_1 - Y_1^{id}) \{ \omega_1 X_1 - (b+m_y) \} + Z_1 \{ \phi_1 (X_1 + \sigma V_1) - (b+m_z) \}. \end{aligned}$$

Since $b+e = (1-p)c/X_1^{id} - \omega_1 Y_1^{id} = pc/V_1^{id}$ and $b+m_y = \omega_1 X_1^{id}$, we can evaluate

$$\begin{aligned} \dot{V}_d &= (1-p)c \left(2 - \frac{X_1^{id}}{X_1} - \frac{X_1}{X_1^{id}} \right) + pc \left(2 - \frac{V_1^{id}}{V_1} - \frac{V_1}{V_1^{id}} \right) \\ &\quad + \phi_1 Z_1 \left(X_1^{id} + \sigma V_1^{id} - \frac{b+m_z}{\phi_1} \right). \end{aligned}$$

We remark that $\phi_1(X_1^{id} + \sigma V_1^{id}) - (b + m_z) \leq 0$ iff $\bar{R}_1^{ip} \leq 1$. In the similar manner, we can show that $\dot{V}_d \leq 0$ because $\bar{R}_1^{ip} \leq 1$. This completes the proof.

(iii) Let us consider the Lyapunov function

$$V_p = X_1 - X_1^{ip} \log X_1 + V_1 - V_1^{ip} \log V_1 + Y_1 + Z_1 - Z_1^{ip} \log Z_1.$$

We have

$$\begin{aligned} \dot{V}_p = & (X_1 - X_1^{ip}) \left\{ \frac{(1-p)c}{X_1} - (b+e) - \omega_1 Y_1 - \phi_1 Z_1 \right\} + (V_1 - V_1^{ip}) \left\{ \frac{pc}{V_1} - (b+e) - \sigma \phi_1 Z_1 \right\} \\ & + Y_1 \{ \omega_1 X_1 - (b + m_y) \} + (Z_1 - Z_1^{ip}) \{ \phi_1 (X_1 + \sigma V_1) - (b + m_z) \}. \end{aligned}$$

Since $b + e = (1-p)c/X_1^{ip} - \phi_1 Z_1^{ip} = pc/V_1^{ip} - \sigma \phi_1 Z_1^{ip}$ and $b + m_z = \phi_1 (X_1^{ip} + \sigma V_1^{ip})$, we can evaluate

$$\dot{V}_p = (1-p)c \left(2 - \frac{X_1^{ip}}{X_1} - \frac{X_1}{X_1^{ip}} \right) + pc \left(2 - \frac{V_1^{ip}}{V_1} - \frac{V_1}{V_1^{ip}} \right) + \omega_1 Y_1 \left(X_1^{ip} - \frac{b + m_y}{\omega_1} \right).$$

We remark that $\omega_1 X_1^{ip} - (b + m_y) \leq 0$ iff $\bar{R}_1^{id} \leq 1$. In the similar manner, we can show that $\dot{V}_p \leq 0$ because $\bar{R}_1^{id} \leq 1$. This completes the proof.

(iv) Let us consider the Lyapunov function

$$V_+ = X_1 - X_1^{i+} \log X_1 + V_1 - V_1^{i+} \log V_1 + Y_1 - Y_1^{i+} \log Y_1 + Z_1 - Z_1^{i+} \log Z_1.$$

Then

$$\begin{aligned} \dot{V}_+ = & (X_1 - X_1^{i+}) \left\{ \frac{(1-p)c}{X_1} - (b+e) - \omega_1 Y_1 - \phi_1 Z_1 \right\} + (V_1 - V_1^{i+}) \left\{ \frac{pc}{V_1} - (b+e) - \sigma \phi_1 Z_1 \right\} \\ & + (Y_1 - Y_1^{i+}) \{ \omega_1 X_1 - (b + m_y) \} + (Z_1 - Z_1^{i+}) \{ \phi_1 (X_1 + \sigma V_1) - (b + m_z) \}. \end{aligned}$$

Since $b + e = (1-p)c/X_1^{i+} - \omega_1 Y_1^{i+} - \phi_1 Z_1^{i+} = pc/V_1^{i+} - \sigma \phi_1 Z_1^{i+}$, $b + m_y = \omega_1 X_1^{i+}$ and $b + m_z = \phi_1 (X_1^{i+} + \sigma V_1^{i+})$, we can evaluate

$$\dot{V}_+ = (1-p)c \left(2 - \frac{X_1^{i+}}{X_1} - \frac{X_1}{X_1^{i+}} \right) + pc \left(2 - \frac{V_1^{i+}}{V_1} - \frac{V_1}{V_1^{i+}} \right) \leq 0.$$

This completes the proof. \square

We can completely classify the dynamics of model (1) by the basic reproductive numbers. Table 1 summarizes the existence and stability conditions of the equilibria in model (1).

	Equilibrium	Existence conditions	Stability conditions
(a) $p = 0$	E_1^{n0}	Always	$R_1^{nd} \leq 1$ and $R_1^{np} \leq 1$
	E_1^{nd}	$1 < R_1^{nd}$	$\bar{R}_1^{np} < 1$
	E_1^{np}	$1 < R_1^{np}$	$\bar{R}_1^{nd} < 1$
(b) $p = 1$	E_1^{c0}	Always	$R_1^{cp} \leq 1$
	E_1^{cp}	$1 < R_1^{cp}$	Always
(c) $0 < p < 1$	E_1^{i0}	Always	$R_1^{id} \leq 1$ and $R_1^{ip} \leq 1$
	E_1^{id}	$1 < R_1^{id}$	$\bar{R}_1^{ip} \leq 1$
	E_1^{ip}	$1 < R_1^{ip}$	$\bar{R}_1^{id} \leq 1$
	E_1^{i+}	$1 < \bar{R}_1^{id}$ and $1 < \bar{R}_1^{ip}$	Always

Table 1: The existence and stability condition of the equilibria in model (1)

2.2 The disease transmission in Area 2

From the classification of the dynamics of model (1) in Table 1, we can easily understand those in Area 2 by analyzing model (2). From the convergence theorem (see *Theorem A.1* of [5]), the global behavior of model (2) is determined by the reduced system;

$$\begin{aligned}
X_2' &= c + eX_1^* - bX_2 - (\omega_2 Y_2 + \phi_2 Z_2)X_2, \\
V_2' &= eV_1^* - bV_2 - \sigma\phi_2 Z_2 V_2, \\
Y_2' &= \omega_2 Y_2 X_2 - (b + m_y)Y_2, \\
Z_2' &= \phi_2 Z_2 (X_2 + \sigma V_2) - (b + m_z)Z_2,
\end{aligned} \tag{6}$$

where X_1^* and V_1^* represent a corresponding equilibrium in model (1). Let $a_1 = c + eX_1^*$ and $a_2 = eV_1^*$, and consider a_1, a_2 as any nonnegative constants. Then model (6) can be considered as a special case of model (1) with $c = a_1 + a_2$, $p = a_2/(a_1 + a_2)$ and $e = 0$. We also divide the analysis into three situations concerned with the vaccination rate as follows;

(a) No vaccination program: $p = 0$ in Area 1

If the vaccination rate $p = 0$ (No vaccination program) in Area 1, then model (6) is

$$\begin{aligned} X_2' &= c + eX_1^* - bX_2 - (\omega_2 Y_2 + \phi_2 Z_2)X_2, \\ V_2' &= -bV_2 - \sigma\phi_2 Z_2 V_2, \\ Y_2' &= \omega_2 Y_2 X_2 - (b + m_y)Y_2, \\ Z_2' &= \phi_2 Z_2 (X_2 + \sigma V_2) - (b + m_z)Z_2. \end{aligned} \quad (7)$$

It is clear that $\lim_{t \rightarrow \infty} V_2(t) = 0$ and this system has the following three possible equilibria:

$$\begin{aligned} E_2^{n0} &= (X_2^{n0}, 0, 0, 0), \text{ where } X_2^{n0} = \frac{c + eX_1^*}{b}; \\ E_2^{nd} &= (X_2^{nd}, 0, Y_2^{nd}, 0), \text{ where } X_2^{nd} = \frac{b + m_y}{\omega_2}, Y_2^{nd} = \frac{c + eX_1^* - bX_2^{nd}}{\omega_2 X_2^{nd}}; \\ E_2^{np} &= (X_2^{np}, 0, 0, Z_2^{np}), \text{ where } X_2^{np} = \frac{b + m_z}{\phi_2}, Z_2^{np} = \frac{c + eX_1^* - bX_2^{np}}{\phi_2 X_2^{np}}. \end{aligned}$$

Here X_1^* represents a corresponding one of X_1^{n0} , X_1^{nd} or X_1^{np} . Further this model is essentially same as model (3) and the dynamics can be completely decided by the following basic reproductive numbers:

$$R_2^{nd} = \frac{\omega_2}{b + m_y} X_2^{n0}, \quad R_2^{np} = \frac{\phi_2}{b + m_z} X_2^{n0}, \quad \bar{R}_2^{nd} = \frac{\omega_2}{b + m_y} X_2^{np}, \quad \bar{R}_2^{np} = \frac{\phi_2}{b + m_z} X_2^{nd}.$$

Clearly E_2^{n0} always exists, E_2^{nd} exists iff $R_2^{nd} > 1$ and E_2^{np} exists iff $R_2^{np} > 1$.

The dynamical properties of model (7) are given by the following theorem:

Theorem 2.4. (i) If $R_2^{nd} \leq 1$ and $R_2^{np} \leq 1$, then E_2^{n0} is GAS.

(ii) If $R_2^{nd} > 1$ and $\bar{R}_2^{np} < 1$, then E_2^{nd} is GAS.

(iii) If $R_2^{np} > 1$ and $\bar{R}_2^{nd} < 1$, then E_2^{np} is GAS.

The proofs of this Theorem are given in [7] (see its Theorem 3.1.).

(b) Complete vaccination program: $p = 1$ in Area 1

If the vaccination rate $p = 1$ (Complete vaccination program) in Area 1, then model (6) is

$$\begin{aligned} X_2' &= c - bX_2 - (\omega_2 Y_2 + \phi_2 Z_2)X_2, \\ V_2' &= eV_1^* - bV_2 - \sigma\phi_2 Z_2 V_2, \\ Y_2' &= \omega_2 Y_2 X_2 - (b + m_y)Y_2, \\ Z_2' &= \phi_2 Z_2 (X_2 + \sigma V_2) - (b + m_z)Z_2. \end{aligned} \quad (8)$$

This system has the following four possible equilibria:

$$\begin{aligned} E_2^{c0} &= (X_2^{c0}, V_2^{c0}, 0, 0), \text{ where } X_2^{c0} = \frac{c}{b}, V_2^{c0} = \frac{eV_1^*}{b}; \\ E_2^{cd} &= (X_2^{cd}, V_2^{cd}, Y_2^{cd}, 0), \text{ where } X_2^{cd} = \frac{b+m_y}{\omega_2}, V_2^{cd} = \frac{eV_1^*}{b}, Y_2^{cd} = \frac{c-bX_2^{cd}}{\omega_2 X_2^{cd}}; \\ E_2^{cp} &= (X_2^{cp}, V_2^{cp}, 0, Z_2^{cp}), \text{ where } X_2^{cp} = \frac{c}{b+\phi_2 Z_2^{cp}}, V_2^{cp} = \frac{eV_1^*}{b+\sigma\phi_2 Z_2^{cp}} \end{aligned}$$

and Z_2^{cp} is the unique root of the following equation:

$$\frac{\phi_2 c}{b+\phi_2 Z_2} + \frac{\sigma\phi_2 eV_1^*}{b+\sigma\phi_2 Z_2} = b+m_z;$$

$$\begin{aligned} E_2^{c+} &= (X_2^{c+}, V_2^{c+}, Y_2^{c+}, Z_2^{c+}), \text{ where } X_2^{c+} = \frac{b+m_y}{\omega_2}, V_2^{c+} = \frac{1}{\sigma} \left(\frac{b+m_z}{\phi_2} - \frac{b+m_y}{\omega_2} \right), \\ Y_2^{c+} &= \frac{1}{\omega_2} \left(\frac{c-bX_2^{c+}}{X_2^{c+}} - \phi_2 Z_2^{c+} \right), Z_2^{c+} = \frac{eV_1^* - bV_2^{c+}}{\sigma\phi_2 V_2^{c+}}. \end{aligned}$$

Here V_1^* represents a corresponding one of V_1^{c0} or V_1^{cp} . This model is also essentially same as model (1) and the dynamics can be completely decided by the following basic reproductive numbers:

$$\begin{aligned} R_2^{cd} &= \frac{\omega_2}{b+m_y} X_2^{c0}, \quad R_2^{cp} = \frac{\phi_2}{b+m_z} X_2^{c0} + \frac{\sigma\phi_2}{b+m_z} V_2^{c0}, \\ \bar{R}_2^{cd} &= \frac{\omega_2}{b+m_y} X_2^{cp}, \quad \bar{R}_2^{cp} = \frac{\phi_2}{b+m_z} X_2^{cd} + \frac{\sigma\phi_2}{b+m_z} V_2^{cd}. \end{aligned}$$

We can also conclude the existence conditions of these equilibria as same as model (1) in the following lemma.

Lemma 2.3. (i) E_2^{c0} always exists in \mathbb{R}_+^4 .

(ii) E_2^{cd} exists in \mathbb{R}_+^4 iff $1 < R_2^{cd}$.

(iii) E_2^{cp} exists in \mathbb{R}_+^4 iff $1 < R_2^{cp}$.

(iv) E_2^{c+} exists in \mathbb{R}_+^4 iff $1 < \bar{R}_2^{cd}$ and $1 < \bar{R}_2^{cp}$.

Further we also remark that $\bar{R}_2^{cd} < 1 < R_2^{cd}$ and $\bar{R}_2^{cp} < 1 < R_2^{cp}$ can not hold simultaneously and the dynamical properties of model (8) are given by the following theorem:

Theorem 2.5. (i) If $R_2^{cd} \leq 1$ and $R_2^{cp} \leq 1$, then E_2^{c0} is GAS.

(ii) If $R_2^{cd} > 1$ and $\bar{R}_2^{cp} \leq 1$, then E_2^{cd} is GAS.

(iii) If $R_2^{cp} > 1$ and $\bar{R}_2^{cd} \leq 1$, then E_2^{cp} is GAS.

(iv) If $\bar{R}_2^{cd} > 1$ and $\bar{R}_2^{cp} > 1$, then E_2^{c+} is GAS.

The proofs of this Theorem are essentially the same as *Theorems 2.3.*

(c) *Incomplete vaccination program: $0 < p < 1$ in Area 1*

If the vaccination rate $0 < p < 1$ (Incomplete vaccination program), then we have to consider system (6) directly. This system has the following four possible equilibria:

$$\begin{aligned} E_2^{i0} &= (X_2^{i0}, V_2^{i0}, 0, 0), \text{ where } X_2^{i0} = \frac{c + eX_1^*}{b}, V_2^{i0} = \frac{eV_1^*}{b}; \\ E_2^{id} &= (X_2^{id}, V_2^{id}, Y_2^{id}, 0), \text{ where } X_2^{id} = \frac{b + m_y}{\omega_2}, V_2^{id} = \frac{eV_1^*}{b}, Y_2^{id} = \frac{c + eX_1^* - bX_2^{id}}{\omega_2 X_2^{id}}; \\ E_2^{ip} &= (X_2^{ip}, V_2^{ip}, 0, Z_2^{ip}), \text{ where } X_2^{ip} = \frac{c + eX_1^*}{b + \phi_2 Z_2^{ip}}, V_2^{ip} = \frac{eV_1^*}{b + \sigma \phi_2 Z_2^{ip}} \end{aligned}$$

and Z_2^{ip} is the unique root of the following equation:

$$\frac{\phi_2(c + eX_1^*)}{b + \phi_2 Z_2} + \frac{\sigma \phi_2 eV_1^*}{b + \sigma \phi_2 Z_2} = b + m_z;$$

$$\begin{aligned} E_2^{i+} &= (X_2^{i+}, V_2^{i+}, Y_2^{i+}, Z_2^{i+}), \text{ where } X_2^{i+} = \frac{b + m_y}{\omega_2}, V_2^{i+} = \frac{1}{\sigma} \left(\frac{b + m_z}{\phi_2} - \frac{b + m_y}{\omega_2} \right), \\ Y_2^{i+} &= \frac{1}{\omega_2} \left(\frac{c + eX_1^* - bX_2^{i+}}{X_2^{i+}} - \phi_2 Z_2^{i+} \right), Z_2^{i+} = \frac{eV_1^* - bV_2^{i+}}{\sigma \phi_2 V_2^{i+}}. \end{aligned}$$

Here X_1^* and V_1^* represents a corresponding pair of X_1^{i0} and V_1^{i0} , X_1^{id} and V_1^{id} , X_1^{ip} and V_1^{ip} or X_1^{i+} and V_1^{i+} . This model is also essentially same as model (1) and the dynamics can be completely decided by the following basic reproductive numbers:

$$\begin{aligned} R_2^{id} &= \frac{\omega_2}{b + m_y} X_2^{i0}, \quad R_2^{ip} = \frac{\phi_2}{b + m_z} X_2^{i0} + \frac{\sigma \phi_2}{b + m_z} V_2^{i0}, \\ \bar{R}_2^{id} &= \frac{\omega_2}{b + m_y} X_2^{ip}, \quad \bar{R}_2^{ip} = \frac{\phi_2}{b + m_z} X_2^{id} + \frac{\sigma \phi_2}{b + m_z} V_2^{id}. \end{aligned}$$

We can also conclude the existence conditions of these equilibria as same as model (1) in the following lemma.

Lemma 2.4. (i) E_2^{i0} always exists in \mathbb{R}_+^4 .

(ii) E_2^{id} exists in \mathbb{R}_+^4 iff $1 < R_2^{id}$.

(iii) E_2^{ip} exists in \mathbb{R}_+^4 iff $1 < R_2^{ip}$.

(iv) E_2^{i+} exists in \mathbb{R}_+^4 iff $1 < \bar{R}_2^{id}$ and $1 < \bar{R}_2^{ip}$.

Further we also remark that $\bar{R}_2^{id} < 1 < R_2^{id}$ and $\bar{R}_2^{ip} < 1 < R_2^{ip}$ can not hold simultaneously and the dynamical properties of model (6) are given by the following theorem:

Theorem 2.6. (i) If $R_2^{id} \leq 1$ and $R_2^{ip} \leq 1$, then E_2^{i0} is GAS.

(ii) If $R_2^{id} > 1$ and $\bar{R}_2^{ip} \leq 1$, then E_2^{id} is GAS.

(iii) If $R_2^{ip} > 1$ and $\bar{R}_2^{id} \leq 1$, then E_2^{ip} is GAS.

(iv) If $\bar{R}_2^{id} > 1$ and $\bar{R}_2^{ip} > 1$, then E_2^{i+} is GAS.

The proofs of this Theorem are essentially the same as *Theorems 2.3.*

We can completely classify the dynamics of model (6) by the basic reproductive numbers. Table 2 summarizes the existence and stability conditions of the equilibria in model (6). Therefore, from Table 1 and Table 2, we can obtain the completely classification of the dynamics of model (2).

	Equilibrium	Existence conditions	Stability conditions
(a) $p = 0$	E_2^{n0}	Always	$R_2^{nd} \leq 1$ and $R_2^{np} \leq 1$
	E_2^{nd}	$1 < R_2^{nd}$	$\bar{R}_2^{np} < 1$
	E_2^{np}	$1 < R_2^{np}$	$\bar{R}_2^{nd} < 1$
(b) $p = 1$	E_2^{c0}	Always	$R_2^{cd} \leq 1$ and $R_2^{cp} \leq 1$
	E_2^{cd}	$1 < R_2^{cd}$	$\bar{R}_2^{cp} \leq 1$
	E_2^{cp}	$1 < R_2^{cp}$	$\bar{R}_2^{cd} \leq 1$
	E_2^{c+}	$1 < \bar{R}_2^{cd}$ and $1 < \bar{R}_2^{cp}$	Always
(c) $0 < p < 1$	E_2^{i0}	Always	$R_2^{id} \leq 1$ and $R_2^{ip} \leq 1$
	E_2^{id}	$1 < R_2^{id}$	$\bar{R}_2^{ip} \leq 1$
	E_2^{ip}	$1 < R_2^{ip}$	$\bar{R}_2^{id} \leq 1$
	E_2^{i+}	$1 < \bar{R}_2^{id}$ and $1 < \bar{R}_2^{ip}$	Always

Table 2: The existence and stability condition of the equilibria in model (6)

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